



## Clinical trial results:

### Phase II single-arm study of first line treatment with gemcitabine and pazopanib in patients with inoperable locally advanced or metastatic biliary tree cancer (cholangiocarcinoma or gallbladder carcinoma)

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2012-001705-24    |
| Trial protocol           | GR                |
| Global end of trial date | 28 September 2018 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 08 November 2019 |
| First version publication date | 08 November 2019 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | HE37/12 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01855724 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Hellenic Cooperative Oncology Group   |
| Sponsor organisation address | M. Hatzikostanti 18, Athens, Greece, 11524  |
| Public contact               | Clinical Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr |
| Scientific contact           | Clinical Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 23 July 2019      |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 28 September 2018 |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of pazopanib combination with gemcitabine (measured as Objective Response Rate) in patients with inoperable locally advanced or metastatic biliary tree carcinoma.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines and the local regulatory requirements.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 15 April 2013 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Greece: 29 |
| Worldwide total number of subjects   | 29         |
| EEA total number of subjects         | 29         |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 10 |
| From 65 to 84 years                       | 18 |
| 85 years and over                         | 1  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled in the study from 28 June 2013 until 15 March 2018 from 10 sites in Greece.

### Pre-assignment

Screening details:

Patients were screened for eligibility before entering the study and signed the informed consent form which was obtained before any study procedure.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|           |                         |
|-----------|-------------------------|
| Arm title | Gemcitabine - Pazopanib |
|-----------|-------------------------|

Arm description:

Gemcitabine (1000mg/m<sup>2</sup>, D1 & 8) - Pazopanib (800mg daily dose) treatment combination was administered in treatment cycles, of 21 day duration per cycle. In the absence of disease progression or significant toxicity, 8 cycles of combination treatment were administered, followed by Pazopanib monotherapy at an 800 mg daily dose. Following 8 cycles of Gemcitabine – Pazopanib treatment, patients continued with Pazopanib monotherapy. Each monotherapy cycle had duration of 21 days. Patients received 800mg Pazopanib orally on a daily basis until disease progression or toxicity that was treated and significantly affected their QoL

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Gemcitabine                      |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Cytotoxic agent Gemcitabine, was administered at an 1000 mg/m<sup>2</sup> dose diluted in 250 ml of N/S, in a 30-minute intravenous infusion on days 1 and 8, every 21 days, for 8 cycles.

|  |           |
|--|-----------|
| Investigational medicinal product name | Pazopanib |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Pazopanib was administered at the dose of 800mg on daily basis for 8 cycles of 21 days duration. In the absence of disease progression or significant toxicity Pazopanib was administered as maintenance treatment (monotherapy) at an 800mg daily dose.

| <b>Number of subjects in period 1</b> | Gemcitabine -<br>Pazopanib |
|---------------------------------------|----------------------------|
| Started                               | 29                         |
| Completed                             | 11                         |
| Not completed                         | 18                         |
| Physician decision                    | 1                          |
| Consent withdrawn by subject          | 2                          |
| Disease progression                   | 7                          |
| Adverse event, non-fatal              | 6                          |
| Death                                 | 1                          |
| Temporary suspension of the trial     | 1                          |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall Trial |
| Reporting group description: - |               |

| Reporting group values | Overall Trial | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 29            | 29    |  |
| Age categorical        |               |       |  |
| Units: Subjects        |               |       |  |
| Adults (18-64 years)   | 10            | 10    |  |
| From 65-84 years       | 18            | 18    |  |
| 85 years and over      | 1             | 1     |  |
| Age continuous         |               |       |  |
| Units: years           |               |       |  |
| median                 | 68.6          |       |  |
| full range (min-max)   | 46.5 to 85.0  | -     |  |
| Gender categorical     |               |       |  |
| Units: Subjects        |               |       |  |
| Female                 | 14            | 14    |  |
| Male                   | 15            | 15    |  |

### Subject analysis sets

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Per Protocol Population |
| Subject analysis set type  | Per protocol            |

Subject analysis set description:

Patients who received at least one full study medication cycle, had an initial disease evaluation and the right histological type of cancer.

| Reporting group values | Per Protocol Population |  |  |
|------------------------|-------------------------|--|--|
| Number of subjects     | 21                      |  |  |
| Age categorical        |                         |  |  |
| Units: Subjects        |                         |  |  |
| Adults (18-64 years)   | 7                       |  |  |
| From 65-84 years       | 13                      |  |  |
| 85 years and over      | 1                       |  |  |
| Age continuous         |                         |  |  |
| Units: years           |                         |  |  |
| median                 | 68.6                    |  |  |
| full range (min-max)   | 46.5 to 85.0            |  |  |
| Gender categorical     |                         |  |  |
| Units: Subjects        |                         |  |  |
| Female                 | 11                      |  |  |
| Male                   | 10                      |  |  |

## End points

### End points reporting groups

|  |                         |
|--|-------------------------|
| Reporting group title  | Gemcitabine - Pazopanib |
| Reporting group description:<br>Gemcitabine (1000mg/m <sup>2</sup> , D1 & 8) - Pazopanib (800mg daily dose) treatment combination was administered in treatment cycles, of 21 day duration per cycle. In the absence of disease progression or significant toxicity, 8 cycles of combination treatment were administered, followed by Pazopanib monotherapy at an 800 mg daily dose. Following 8 cycles of Gemcitabine - Pazopanib treatment, patients continued with Pazopanib monotherapy. Each monotherapy cycle had duration of 21 days. Patients received 800mg Pazopanib orally on a daily basis until disease progression or toxicity that was treated and significantly affected their QoL |                         |
| Subject analysis set title   | Per Protocol Population |
| Subject analysis set type  | Per protocol            |
| Subject analysis set description:<br>Patients who received at least one full study medication cycle, had an initial disease evaluation and the right histological type of cancer.  |                         |

### Primary: Objective response Rate

|   |  |
|---|--|
| End point title   | Objective response Rate <sup>[1]</sup> |
| End point description:<br>Objective response rate was defined as the percentage of patients with a confirmed complete (CR) or partial response (PR) as per RECIST 1.1 criteria. |  |
| End point type  | Primary                                |
| End point timeframe:<br>Imaging evaluation for the determination of tumor response was performed every 8 weeks.   |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The objective response rate, i.e. the percentage of patients achieving a complete or partial response as the best response was described using descriptive statistics for the ITT and the PP population

| End point values                         | Gemcitabine - Pazopanib | Per Protocol Population |  |  |
|--|-------------------------|-------------------------|--|--|
| Subject group type                       | Reporting group         | Subject analysis set    |  |  |
| Number of subjects analysed              | 29                      | 21                      |  |  |
| Units: percentage of patients with CR/PR |                         |                         |  |  |
| Objective response rate (%)              | 14                      | 19                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival

|   |                           |
|---|---------------------------|
| End point title   | Progression Free Survival |
| End point description:<br>Progression Free Survival was calculated from the date of patient's entry into the study until the first documented disease progression, death or last contact, whichever occurred first. |                           |
| End point type  | Secondary                 |

End point timeframe:

Patients were followed up for a median of 25.8 months (95% CI 13.5-25.8).

| End point values                 | Gemcitabine - Pazopanib |  |  |  |
|----------------------------------|-------------------------|--|--|--|
| Subject group type               | Reporting group         |  |  |  |
| Number of subjects analysed      | 29                      |  |  |  |
| Units: months                    |                         |  |  |  |
| median (confidence interval 95%) | 6.3 (2.3 to 8.0)        |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

|  |                  |
|--|------------------|
| End point title  | Overall Survival |
| End point description:   |                  |
| Overall Survival was calculated from the date of patient's entry into the study until death or last contact. |                  |
| End point type   | Secondary        |
| End point timeframe:   |                  |
| Patients were followed up for a median of 25.8 months (95% CI 13.5-25.8).                                    |                  |

| End point values                 | Gemcitabine - Pazopanib |  |  |  |
|----------------------------------|-------------------------|--|--|--|
| Subject group type               | Reporting group         |  |  |  |
| Number of subjects analysed      | 29                      |  |  |  |
| Units: months                    |                         |  |  |  |
| median (confidence interval 95%) | 10.4 (7.3 to 13.4)      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety

|  |           |
|--|-----------|
| End point title  | Safety    |
| End point description:   |           |
| Safety was assessed in the safety population consisting of all patients that received at least one dose of the study drug (s). |           |
| End point type   | Secondary |

End point timeframe:

Evaluation of Adverse Events (AEs) was performed every 21 days (per treatment cycle) throughout the course of treatment.

| End point values            | Gemcitabine - Pazopanib |  |  |  |
|-----------------------------|-------------------------|--|--|--|
| Subject group type          | Reporting group         |  |  |  |
| Number of subjects analysed | 29                      |  |  |  |
| Units: number of patients   |                         |  |  |  |
| Any adverse event           | 29                      |  |  |  |
| Fatal adverse event         | 1                       |  |  |  |
| Serious adverse event       | 13                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of Life

|   |                 |
|---|-----------------|
| End point title   | Quality of Life |
| End point description:<br>The Quality of Life (QoL) was assessed using the EUROQOL 5D questionnaire that consists of 5 dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression and the EQ-VAS measuring the patient's health status in a scale of 0 to 100 with 0 indicating the worst health and 100 corresponding to the best health, as rated by the patient. |                 |
| End point type  | Secondary       |
| End point timeframe:<br>The EUROQOL 5D Questionnaire was completed before treatment initiation, every 8 weeks and post treatment.   |                 |

| End point values                     | Gemcitabine - Pazopanib |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 28 <sup>[2]</sup>       |  |  |  |
| Units: EQ-VAS                        |                         |  |  |  |
| arithmetic mean (standard deviation) |                         |  |  |  |
| Baseline                             | 55 (± 31.3)             |  |  |  |
| Last treatment cycle                 | 54.1 (± 30.2)           |  |  |  |

Notes:

[2] - 28 patients completed the EQ-5D questionnaire at baseline and 23 at their last cycle of treatment.

### Statistical analyses

No statistical analyses for this end point

### Secondary: 6-month Progression Free Survival Rate



|   |  |
|---|--|
| End point title   | 6-month Progression Free Survival Rate |
| End point description:<br>The percentage of patients surviving 6 months post study entry.         |  |
| End point type  | Secondary                              |
| End point timeframe:<br>Patients were followed up for a median of 25.8 months (95% CI 13.5-25.8). |  |

|                               |                         |  |  |  |
|-------------------------------|-------------------------|--|--|--|
| <b>End point values</b>       | Gemcitabine - Pazopanib |  |  |  |
| Subject group type            | Reporting group         |  |  |  |
| Number of subjects analysed   | 29                      |  |  |  |
| Units: percentage of patients | 52                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Upon signature of the ICF up to 30 days after the last administration of Pazopanib. Following the 30 day EOT visit all ongoing SAEs as well as ongoing related AEs and new related SAEs were collected and followed till resolution/stabilisation/new treatment

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Gemcitabine - Pazopanib |
|-----------------------|-------------------------|

Reporting group description:

The combination was administered as follows: Gemcitabine 1000mg/m<sup>2</sup> i.v on days 1 and 8 with Pazopanib 800mg daily dose per os on days 1-21, every 21 days for 8 cycles followed by Pazopanib monotherapy 800mg daily dose per os in days 1-21 every 21 days until disease progression was occurred or unacceptable toxicity.

| Serious adverse events                            | Gemcitabine - Pazopanib   |  |  |
|---|---|--|--|
| Total subjects affected by serious adverse events |   |  |  |
| subjects affected / exposed                       | 13 / 29 (44.83%)  |  |  |
| number of deaths (all causes)                     | 25  |  |  |
| number of deaths resulting from adverse events    | 1   |  |  |
| Investigations                                    |   |  |  |
| Alanine aminotransferase increased                |   |  |  |
| subjects affected / exposed                       | 3 / 29 (10.34%)   |  |  |
| occurrences causally related to treatment / all   | 2 / 3   |  |  |
| deaths causally related to treatment / all        | 0 / 0   |  |  |
| Aspartate aminotransferase increased              |   |  |  |
| subjects affected / exposed                       | 3 / 29 (10.34%)   |  |  |
| occurrences causally related to treatment / all   | 2 / 3   |  |  |
| deaths causally related to treatment / all        | 0 / 0   |  |  |
| Gamma-glutamyltransferase increased               |   |  |  |
| subjects affected / exposed                       | 2 / 29 (6.90%)  |  |  |
| occurrences causally related to treatment / all   | 2 / 2   |  |  |
| deaths causally related to treatment / all        | 0 / 0   |  |  |
| Alkaline Phosphatase increased                    | Additional description: increased level of alkaline phosphatase in a blood specimen |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 1 / 29 (3.45%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Blood bilirubin increased                       |   |  |  |
| subjects affected / exposed                     | 3 / 29 (10.34%)   |  |  |
| occurrences causally related to treatment / all | 0 / 3   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Vascular disorders                              |   |  |  |
| Hypertension                                    |   |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Nervous system disorders                        |   |  |  |
| Ischaemic stroke                                |   |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Gastrointestinal disorders                      |   |  |  |
| Abdominal pain                                  |   |  |  |
| subjects affected / exposed                     | 2 / 29 (6.90%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Diarrhoea                                       |   |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Ileus   |   |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| jejunal hemorrhage                              | Additional description: Bleeding from the jejunal wall. |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Lung abscess                                    |                |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cholangitis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholecystitis                                   |                |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| hepatic coma                                    |                |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Acute kidney injury                             |                |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Lung infection                                  |                |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatic infection                               |                |  |  |
| subjects affected / exposed                     | 1 / 29 (3.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

| <b>Non-serious adverse events</b>                     | Gemcitabine - Pazopanib |  |  |
|---|-------------------------|--|--|
| Total subjects affected by non-serious adverse events |                         |  |  |
| subjects affected / exposed                           | 28 / 29 (96.55%)        |  |  |
| Vascular disorders                                    |                         |  |  |
| Hypertension  |                         |  |  |
| subjects affected / exposed                           | 15 / 29 (51.72%)        |  |  |
| occurrences (all)                                     | 32                      |  |  |
| General disorders and administration site conditions  |                         |  |  |
| edema face  |                         |  |  |
| alternative dictionary used: CTCAE 4.03               |                         |  |  |
| subjects affected / exposed                           | 1 / 29 (3.45%)          |  |  |
| occurrences (all)                                     | 1                       |  |  |
| edema limbs   |                         |  |  |
| alternative dictionary used: CTCAE 4.03               |                         |  |  |
| subjects affected / exposed                           | 4 / 29 (13.79%)         |  |  |
| occurrences (all)                                     | 5                       |  |  |
| Fatigue   |                         |  |  |
| subjects affected / exposed                           | 16 / 29 (55.17%)        |  |  |
| occurrences (all)                                     | 21                      |  |  |
| fever   |                         |  |  |
| alternative dictionary used: CTCAE 4.03               |                         |  |  |
| subjects affected / exposed                           | 3 / 29 (10.34%)         |  |  |
| occurrences (all)                                     | 6                       |  |  |
| other - voice disorders                               |                         |  |  |
| alternative dictionary used: CTCAE 4.03               |                         |  |  |
| subjects affected / exposed                           | 1 / 29 (3.45%)          |  |  |
| occurrences (all)                                     | 1                       |  |  |
| Pain  |                         |  |  |
| subjects affected / exposed                           | 1 / 29 (3.45%)          |  |  |
| occurrences (all)                                     | 1                       |  |  |
| Respiratory, thoracic and mediastinal disorders       |                         |  |  |
| Rhinitis allergic                                     |                         |  |  |
| subjects affected / exposed                           | 1 / 29 (3.45%)          |  |  |
| occurrences (all)                                     | 1                       |  |  |
| Cough   |                         |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed             | 1 / 29 (3.45%)   |  |  |
| occurrences (all)                       | 1                |  |  |
| Dyspnoea                                |                  |  |  |
| subjects affected / exposed             | 2 / 29 (6.90%)   |  |  |
| occurrences (all)                       | 2                |  |  |
| Epistaxis                               |                  |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)   |  |  |
| occurrences (all)                       | 1                |  |  |
| other - pharyngolaryngeal pain          |                  |  |  |
| alternative dictionary used: CTCAE 4.03 |                  |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)   |  |  |
| occurrences (all)                       | 1                |  |  |
| Psychiatric disorders                   |                  |  |  |
| Anxiety                                 |                  |  |  |
| subjects affected / exposed             | 2 / 29 (6.90%)   |  |  |
| occurrences (all)                       | 2                |  |  |
| other - distress                        |                  |  |  |
| alternative dictionary used: CTCAE 4.03 |                  |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)   |  |  |
| occurrences (all)                       | 1                |  |  |
| Investigations                          |                  |  |  |
| White blood cell count decreased        |                  |  |  |
| subjects affected / exposed             | 24 / 29 (82.76%) |  |  |
| occurrences (all)                       | 79               |  |  |
| Neutrophil count decreased              |                  |  |  |
| subjects affected / exposed             | 24 / 29 (82.76%) |  |  |
| occurrences (all)                       | 71               |  |  |
| Alanine aminotransferase increased      |                  |  |  |
| subjects affected / exposed             | 15 / 29 (51.72%) |  |  |
| occurrences (all)                       | 32               |  |  |
| alkaline phosphatase increased          |                  |  |  |
| alternative dictionary used: CTCAE 4.03 |                  |  |  |
| subjects affected / exposed             | 8 / 29 (27.59%)  |  |  |
| occurrences (all)                       | 11               |  |  |
| Aspartate aminotransferase increased    |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                   | 13 / 29 (44.83%) |  |  |
| occurrences (all)                             | 22               |  |  |
| Blood bilirubin increased                     |                  |  |  |
| subjects affected / exposed                   | 8 / 29 (27.59%)  |  |  |
| occurrences (all)                             | 13               |  |  |
| cholesterol high                              |                  |  |  |
| alternative dictionary used: CTCAE 4.03       |                  |  |  |
| subjects affected / exposed                   | 3 / 29 (10.34%)  |  |  |
| occurrences (all)                             | 5                |  |  |
| creatinine increased                          |                  |  |  |
| alternative dictionary used: CTCAE 4.03       |                  |  |  |
| subjects affected / exposed                   | 3 / 29 (10.34%)  |  |  |
| occurrences (all)                             | 3                |  |  |
| Gamma-glutamyltransferase increased           |                  |  |  |
| subjects affected / exposed                   | 8 / 29 (27.59%)  |  |  |
| occurrences (all)                             | 10               |  |  |
| other - lactate dehydrogenase serum increased |                  |  |  |
| alternative dictionary used: CTCAE 4.03       |                  |  |  |
| subjects affected / exposed                   | 1 / 29 (3.45%)   |  |  |
| occurrences (all)                             | 1                |  |  |
| Lymphocyte count decreased                    |                  |  |  |
| subjects affected / exposed                   | 4 / 29 (13.79%)  |  |  |
| occurrences (all)                             | 11               |  |  |
| Platelet count decreased                      |                  |  |  |
| subjects affected / exposed                   | 12 / 29 (41.38%) |  |  |
| occurrences (all)                             | 30               |  |  |
| Amylase increased                             |                  |  |  |
| subjects affected / exposed                   | 1 / 29 (3.45%)   |  |  |
| occurrences (all)                             | 1                |  |  |
| Cardiac disorders                             |                  |  |  |
| Sinus bradycardia                             |                  |  |  |
| subjects affected / exposed                   | 1 / 29 (3.45%)   |  |  |
| occurrences (all)                             | 2                |  |  |
| Sinus tachycardia                             |                  |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 29 (3.45%)<br>1 |  |  |
| Nervous system disorders                         |                     |  |  |
| Dizziness  |                     |  |  |
| subjects affected / exposed                      | 2 / 29 (6.90%)      |  |  |
| occurrences (all)                                | 3                   |  |  |
| Dysgeusia  |                     |  |  |
| subjects affected / exposed                      | 2 / 29 (6.90%)      |  |  |
| occurrences (all)                                | 3                   |  |  |
| Sleep disorder                                   |                     |  |  |
| subjects affected / exposed                      | 1 / 29 (3.45%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Neuropathy peripheral                            |                     |  |  |
| subjects affected / exposed                      | 1 / 29 (3.45%)      |  |  |
| occurrences (all)                                | 2                   |  |  |
| Blood and lymphatic system disorders             |                     |  |  |
| Anaemia  |                     |  |  |
| subjects affected / exposed                      | 12 / 29 (41.38%)    |  |  |
| occurrences (all)                                | 17                  |  |  |
| Eye disorders                                    |                     |  |  |
| other - eyelash oedema                           |                     |  |  |
| alternative dictionary used: CTCAE 4.03          |                     |  |  |
| subjects affected / exposed                      | 1 / 29 (3.45%)      |  |  |
| occurrences (all)                                | 2                   |  |  |
| watering eye                                     |                     |  |  |
| alternative dictionary used: CTCAE 4.03          |                     |  |  |
| subjects affected / exposed                      | 1 / 29 (3.45%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Gastrointestinal disorders                       |                     |  |  |
| Abdominal pain                                   |                     |  |  |
| subjects affected / exposed                      | 7 / 29 (24.14%)     |  |  |
| occurrences (all)                                | 12                  |  |  |
| Ascites  |                     |  |  |
| subjects affected / exposed                      | 1 / 29 (3.45%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Constipation                                     |                     |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed             | 2 / 29 (6.90%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Diarrhoea                               |                 |  |  |
| subjects affected / exposed             | 8 / 29 (27.59%) |  |  |
| occurrences (all)                       | 14              |  |  |
| Dyspepsia                               |                 |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Oesophageal haemorrhage                 |                 |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Reflux gastritis                        |                 |  |  |
| subjects affected / exposed             | 2 / 29 (6.90%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Haematochezia                           |                 |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| other - epigastric pain                 |                 |  |  |
| alternative dictionary used: CTCAE 4.03 |                 |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| other - mucosal defecation              |                 |  |  |
| alternative dictionary used: CTCAE 4.03 |                 |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Stomatitis                              |                 |  |  |
| subjects affected / exposed             | 3 / 29 (10.34%) |  |  |
| occurrences (all)                       | 3               |  |  |
| Nausea                                  |                 |  |  |
| subjects affected / exposed             | 8 / 29 (27.59%) |  |  |
| occurrences (all)                       | 13              |  |  |
| Periodontal disease                     |                 |  |  |
| subjects affected / exposed             | 1 / 29 (3.45%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Vomiting                                |                 |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 7 / 29 (24.14%)<br>9 |  |  |
| Skin and subcutaneous tissue disorders             |                      |  |  |
| Alopecia   |                      |  |  |
| subjects affected / exposed                        | 1 / 29 (3.45%)       |  |  |
| occurrences (all)                                  | 1                    |  |  |
| Dry skin   |                      |  |  |
| subjects affected / exposed                        | 1 / 29 (3.45%)       |  |  |
| occurrences (all)                                  | 1                    |  |  |
| Acne   |                      |  |  |
| subjects affected / exposed                        | 2 / 29 (6.90%)       |  |  |
| occurrences (all)                                  | 2                    |  |  |
| Palmar-plantar erythrodysaesthesia<br>syndrome     |                      |  |  |
| subjects affected / exposed                        | 1 / 29 (3.45%)       |  |  |
| occurrences (all)                                  | 1                    |  |  |
| Hair colour changes                                |                      |  |  |
| subjects affected / exposed                        | 2 / 29 (6.90%)       |  |  |
| occurrences (all)                                  | 2                    |  |  |
| Skin hyperpigmentation                             |                      |  |  |
| subjects affected / exposed                        | 1 / 29 (3.45%)       |  |  |
| occurrences (all)                                  | 1                    |  |  |
| Renal and urinary disorders                        |                      |  |  |
| Haematuria   |                      |  |  |
| subjects affected / exposed                        | 1 / 29 (3.45%)       |  |  |
| occurrences (all)                                  | 1                    |  |  |
| Proteinuria  |                      |  |  |
| subjects affected / exposed                        | 6 / 29 (20.69%)      |  |  |
| occurrences (all)                                  | 8                    |  |  |
| Endocrine disorders                                |                      |  |  |
| Hypothyroidism                                     |                      |  |  |
| subjects affected / exposed                        | 2 / 29 (6.90%)       |  |  |
| occurrences (all)                                  | 2                    |  |  |
| Musculoskeletal and connective tissue<br>disorders |                      |  |  |
| Arthralgia   |                      |  |  |
| subjects affected / exposed                        | 1 / 29 (3.45%)       |  |  |
| occurrences (all)                                  | 1                    |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 29 (3.45%)<br>1  |  |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 29 (3.45%)<br>1  |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 1 / 29 (3.45%)<br>1  |  |  |
| Infections and infestations<br>Cholangitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 29 (3.45%)<br>1  |  |  |
| Papulopustular rash<br>alternative dictionary used: CTCAE 4.03<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 29 (3.45%)<br>1  |  |  |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 29 (3.45%)<br>1  |  |  |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)   | 1 / 29 (3.45%)<br>1  |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)   | 2 / 29 (6.90%)<br>2  |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)   | 2 / 29 (6.90%)<br>2  |  |  |
| Metabolism and nutrition disorders<br>other - anorexia<br>alternative dictionary used: CTCAE 4.03<br>subjects affected / exposed<br>occurrences (all) | 4 / 29 (13.79%)<br>5 |  |  |
| Hyperglycaemia  |                      |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 6 / 29 (20.69%) |  |  |
| occurrences (all)           | 16              |  |  |
| Hyperkalaemia               |                 |  |  |
| subjects affected / exposed | 2 / 29 (6.90%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Hypermagnesaemia            |                 |  |  |
| subjects affected / exposed | 1 / 29 (3.45%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hypernatraemia              |                 |  |  |
| subjects affected / exposed | 1 / 29 (3.45%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hypertriglyceridaemia       |                 |  |  |
| subjects affected / exposed | 2 / 29 (6.90%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Hypoalbuminaemia            |                 |  |  |
| subjects affected / exposed | 5 / 29 (17.24%) |  |  |
| occurrences (all)           | 7               |  |  |
| Hypocalcaemia               |                 |  |  |
| subjects affected / exposed | 4 / 29 (13.79%) |  |  |
| occurrences (all)           | 6               |  |  |
| Hypoglycaemia               |                 |  |  |
| subjects affected / exposed | 1 / 29 (3.45%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hypokalaemia                |                 |  |  |
| subjects affected / exposed | 4 / 29 (13.79%) |  |  |
| occurrences (all)           | 7               |  |  |
| Hypomagnesaemia             |                 |  |  |
| subjects affected / exposed | 1 / 29 (3.45%)  |  |  |
| occurrences (all)           | 4               |  |  |
| Hyponatraemia               |                 |  |  |
| subjects affected / exposed | 6 / 29 (20.69%) |  |  |
| occurrences (all)           | 7               |  |  |
| Hypophosphataemia           |                 |  |  |
| subjects affected / exposed | 2 / 29 (6.90%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Hyperphosphataemia          |                 |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 29 (6.90%) |  |  |
| occurrences (all)           | 2              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 12 September 2017 | <p>Amendment of the inclusion criteria 3 and 6: Criterion 3: Histologic or cytologic diagnosis of cholangiocarcinoma (intrahepatic or extrahepatic biliary adenocarcinoma, gallbladder adenocarcinoma and periampullary bile duct adenocarcinoma).</p> <p>Criterion 6: No previous administration of other chemotherapy or targeted therapy. By exception, patients with primary lesion that was removed in the past and received adjuvant chemotherapy with gemcitabine, with the last dose being administered at least 1 year prior the patient's inclusion date in this protocol, are acceptable.</p> <p>Pages 23-25: Pazopanib (Votrient®) available for the study from its initiation onwards is available in white 200mg tablets (34 in each bottle) compared to the pink, commercially available, tablets. The stock for this IMP expires in November 2017 and will be used to cover the needs of the study patients until stock-out and as per its expiry date. Then, pazopanib (Votrient®) supplied in the study, will be the 200mg commercially available product (pink tablets, 90 in each bottle), in its commercial packaging with appropriate labelling for use in the clinical trial.</p> <p>Packaging and labelling of the commercially available medicinal product to be used in the clinical trial will be performed by Novartis as per GMP, ICH/GCP and local law requirements. Labels will include the necessary information in Greek, will comply with applicable legislation and will not provide any patient information. Pazopanib will be dispensed to patients for home use at each study visit from the study physician/designated site personnel. Each package will contain sufficient drug supply until the patient's next visit. Study drug will be received by a delegated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and delegated site personnel have access.</p> <p>Upon receipt, pazopanib should be stored according to the instructions on the drug label.</p> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption  | Restart date |
|--------------|---|--------------|
| 22 July 2013 | For safety reasons, upon a request from Glaxo Smith Kline, in clinical studies investigating the combination of Gemcitabine – Pazopanib the enrollment was suspended. | 05 May 2014  |

Notes:

### Limitations and caveats

None reported